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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,026	07/30/2001	Rosanne M. Crooke	ISPH-0588	1035

36441 7590 07/27/2005

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EXAMINER	
GIBBS, TERRA C	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/918,026	CROOKE ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10,12 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/21/05*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☒ Other: *Sequence comparison alignment*.

DETAILED ACTION

This Office Action is a response to Applicants Amendment and Remarks filed May 16, 2005.

Claim 1 has been amended. Claims 1, 4-10, 12 and 13 are pending in the instant application.

Claims 1, 4-10, 12 and 13 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

Applicants Information Disclosure Statement filed January 21, 2005 is acknowledged. The information referred to therein have been considered on the merits.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed November 18, 2004, claims 1, 4-10, 12, and 13 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is withdrawn** in view of Applicants amendment to the claims filed May 16, 2005 to correct for insufficient antecedent basis.

In the previous Office Action mailed November 18, 2004, claims 1, 4-10, 12, and 13 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. **This rejection is withdrawn** in view of Applicants amendment to the claims filed May 16, 2005 to recite "a coding region" instead of "the coding region".

Claim Rejections - 35 USC § 102

In the previous Office Action mailed November 18, 2004, claims 1 and 12 were rejected under 35 U.S.C. 102(e) as being anticipated by Cases et al. [U.S. Patent No. 6,579,974]. **This rejection is withdrawn** in view of Applicants amendment to the claims and Applicant's Declaration pursuant to Rule 1.132 filed May 16, 2005. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Declaration, which shows that the primer described by Cases does not inhibit ACAT-2 expression by at least 60% as now recited in claim 1.

In the previous Office Action mailed November 18, 2004, claims 1, 4-10, 12, and 13 were rejected under 35 U.S.C. 102(e) as being anticipated by Cowsert et al. [U.S. Patent No. 6,482,644]. **This rejection is withdrawn** in view of Applicants amendment to the claims and Applicant's Declaration pursuant to Rule 1.132 filed May 16, 2005. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Declaration

which shows that the antisense oligonucleotide described by Cowsert et al. does not inhibit ACAT-2 expression by at least 60% as now recited in claim 1.

In the previous Office Action mailed November 18, 2004, claims 1, 4-10, 12, and 13 were rejected under 35 U.S.C. 102(b) as being anticipated by Dean et al. [U.S. Patent No. 6,180,353]. **This rejection is withdrawn** in view of Applicants amendment to the claims and Applicant's Declaration pursuant to Rule 1.132 filed May 16, 2005. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Declaration which shows that the antisense oligonucleotide described by Dean et al. does not inhibit ACAT-2 expression by at least 60% as now recited in claim 1.

In the previous Office Action mailed November 18, 2004, claims 1, 4-10, 12, and 13 were rejected under 35 U.S.C. 102(e) as being anticipated by Zhang et al. [U.S. Patent No. 6,503,754]. **This rejection is withdrawn** in view of Applicants amendment to the claims and Applicant's Declaration pursuant to Rule 1.132 filed May 16, 2005. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Declaration which shows that the antisense oligonucleotide described by Zhang et al. does not inhibit ACAT-2 expression by at least 60% as now recited in claim 1.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed November 18, 2004, claims 1, 4-10, 12, and 13 were rejected under 35 U.S.C. 103(a) as being unpatentable over Oelkers et al. (Journal of Biological Chemistry, 1998 Vol. 273:26765-26771) [Applicants IDS reference BA, submitted November 19, 2002] in view of Chong et al. (Drugs, 2000 Vol. 60:55-93) [Applicants IDS reference AL, submitted November 19, 2002], and Bennett et al. [U.S. Patent No. 6,613,567]. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed November 18, 2004.

Response to Arguments

In response to this rejection, Applicants argue that a proper *prima facie* case has not been established because the combination of Oelkers et al., Chong et al., and Bennett et al. does not provide sufficient motivation to create an inhibitor which targets human acyl-CoA cholesterol acyltransferase-2 (ACAT-2) mRNA of SEQ ID NO:3 as claimed in the instant application. Applicants also argue that neither does the combination of Chong et al., Oelkers et al., and Bennett et al. teach all the limitations of the claimed invention. Applicants argue that the three basic criteria of obviousness have not been met.

First, Applicants argue that Chong et al. describe efforts in designing inhibitors targeting ACAT proteins to treat and prevent atherosclerosis. However, Applicants argue that Chong et al. also state, "whether inhibition of ACAT will prevent

atherosclerosis is not yet clear". Applicants contend that Chong et al. do not describe inhibitors which target ACAT-2 mRNA of SEQ ID NO:3 as claimed.

Second, Applicants argue that Oelkers et al. describes the human acyl-CoA cholesterol (ACAT-1) and (ACAT-2) isoforms and their respective cDNAs. However, Applicants contend that Oelkers et al. do not elucidate with any certainty functional distinctions between the two ACAT protein isoforms. Applicants also argue that Oelkers et al. do not describe the mRNA sequence of ACAT-2 of SEQ ID NO:3.

Third, Applicants argue that Bennett et al. is directed to antisense targeting HER-2, a gene unrelated to ACAT-2.

Finally, Applicants argue that there is no suggestion or motivation contained in the combination of Oelkers et al., Chong et al., and Bennett et al. because there is no teaching of functional differences between the two ACAT protein isoforms, an advantage of designing an inhibitor of ACAT-2, nor a description of inhibiting ACAT-2 mRNA of SEQ ID NO:3. Applicants contend that the suggestion or motivation to make an antisense inhibitor of ACAT-2 mRNA was first described by the Applicants in the present application.

Applicant's arguments have been fully considered but are not found persuasive because Applicant argues against the three cited references individually, but must consider the rejection based upon the combination of the references. *See* MPEP 2145, section IV. In totality, the references of Oelkers et al., Chong et al., and Bennett et al. render the instant application obvious and demonstrate that one of ordinary skill in the art would have been motivated and expected success in making the current invention at

the time of filing. Regarding Applicant's first argument, Chong et al. clearly provide motivation to make ACAT inhibitors at page 73, second full paragraph, where it states, **"Overall, the use of ACAT inhibitors in the future appear promising"**. Chong et al. also discuss that existing small molecule inhibitors of ACAT have poor gastrointestinal tract tolerability in humans and thus provide motivation to make other inhibitors of ACAT which overcome this problem. Although Chong et al. state, "whether inhibition of ACAT will prevent atherosclerosis is not yet clear", Chong et al. also state, "ACAT inhibitors reduce fat and cholesterol absorption" (see page 84, second column, second paragraph) which are clearly involved in atherogenesis. Though Chong et al. do not explicitly describe inhibitors which target ACAT-2 mRNA of SEQ ID NO:3 as claimed, Oelkers et al. describes the human acyl-CoA cholesterol acyltransferase-2 (ACAT-2) cDNA and Bennett et al. teach how to design antisense compounds to different target regions of a known gene to inhibit gene expression at various capacities. In this regard, one of ordinary skill in the art would have expected success in using the teachings of Bennett et al. and apply them to making an antisense oligonucleotide targeted to human acyl-CoA cholesterol acyltransferase-2 (ACAT-2) (SEQ ID NO:3) as instantly claimed since it is well known and routine in the art to make antisense oligonucleotides to a known gene to probe for gene function.

Regarding Applicant's second argument, Applicants contend that Oelkers et al. do not describe the mRNA sequence of ACAT-2 of SEQ ID NO:3 of the instant invention, however this is not found persuasive because a comparison of SEQ ID NO:3 of the instant invention (GenBank Accession No. AF099031) and the full length human

acyl-CoA cholesterol acyltransferase-2 (ACAT-2) sequence taught by Oelkers et al. (GenBank Accession No. AF059203) reveals that the two sequences are almost 100% identical (see attached sequence alignment). Therefore, Oelkers et al. clearly describe the mRNA sequence of ACAT-2 of the instant claims.

Applicants also contend that Oelkers et al. do not elucidate with any certainty functional distinctions between the two ACAT protein isoforms, however this is not found persuasive because the elucidation of functional distinctions between ACAT-1 and ACAT-2 is not a requirement of the instant claims. The instant claims are drawn to an antisense oligonucleotide targeted to the coding region of a nucleic acid molecule encoding human acyl-CoA cholesterol acyltransferase-2 (ACAT-2) (SEQ ID NO:3). Nowhere do the claims require that the antisense oligonucleotide target one ACAT isoform over another, for example.

Regarding Applicant's third argument, Applicants argue that Bennett et al. is directed to antisense targeting HER-2, a gene unrelated to ACAT-2. Bennett et al. was relied upon to teach that following generic teachings, one of ordinary skill in the art would have expected success in making antisense oligonucleotides to a known target gene.

In summary, it would have been obvious to one of ordinary skill in the art to design an inhibitor of ACAT since Chong et al. provide clear motivation to do such in their statement, "Overall, the use of ACAT inhibitors in the future appear promising". One of ordinary skill in the art would have envisioned specific inhibitors of ACAT-2 since at the time Chong et al. made their statement, and at the time of filing of the instant

invention, it was well known in the art that ACAT isofoms consisted of ACAT-1 and ACAT-2. One of ordinary skill would have been motivated to make antisense oligonucleotide inhibitors of ACAT since Chong et al. taught small molecule inhibitors of ACAT have poor gastrointestinal tract tolerability in humans, thus providing motivation to make other inhibitors of ACAT, which overcome this problem. One of ordinary skill in the art would have expected success in making antisense oligonucleotides targeted to a nucleic acid encoding human acyl-CoA cholesterol acyltransferase-2 (ACAT-2) since Bennett taught the design of antisense oligonucleotides targeted to different regions of a known target gene with a wide range of inhibition capacities and Oelkers et al. taught the sequence of the human acyl-CoA cholesterol acyltransferase-2 (ACAT-2) gene. One of ordinary skill in the art would have expected success in making antisense oligonucleotides that hybridize to human acyl-CoA cholesterol acyltransferase-2 (ACAT-2) (SEQ ID NO:3) and inhibit expression by at least 60% as now recited in claim 1 since Bennett et al. demonstrate that following generic teachings of making antisense oligonucleotides to a known target gene, it would be expected that oligonucleotides will inhibit by at least 60% since a wide range of oligonucleotides of various inhibition capacities are created (see Bennett et al. Tables 2 and 4). Further, Taylor et al. (Drug Discovery Today, 1999 Vol. 4:562-567) teach at page 565, first few lines that screening 3-6 oligomers per target is sufficient to find one that inhibits the gene with 66-95% efficiency.

Therefore, the invention of claims 1, 4-10, 12, and 13 would have been obvious to one of ordinary skill in the art, as a whole, at the time the instant invention was made.

Applicant's amendment necessitated the new ground(s) of rejection presented below:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-10, 12, and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The amendment filed May 16, 2005 introduces new matter into the disclosure because it recites the limitation, "inhibits the expression of a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 by at least 60%". There is no support in the instant specification as filed for inhibiting the expression of acyl CoA cholesterol acyltransferase-2 by at least 60%.

The response filed May 16, 2005 indicates that support for the limitation, "inhibits the expression of a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 by at least 60%" is present throughout the specification and claims as originally filed. It is noted that the instant specification at Table 1 on page 87 shows

approximately 23 specific antisense oligonucleotides which inhibit expression of acyl CoA cholesterol acyltransferase-2 from 0% to 89%. Additionally, page 87, lines 29-33 recites, "As shown in Table 1, SEQ ID NOs: 21, 23, 24, 25, 25, 28, 29, 30, 31, 33, 34, 35, 36, 36, and 38 demonstrated at least 40% inhibition of human acyl CoA cholesterol acyltransferase-2 expression". It appears that Applicants have support for the limitation, "inhibits the expression of a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 by at least 40%", as demonstrated in Table 1. However, it does not appear that Table 1, nor any other part of the instant specification supports the limitation, "inhibits the expression of a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 by at least 60%". Therefore the limitation "inhibits the expression of a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 by at least 60%" is a new matter issue.

Applicant should **specifically** point out the support for any amendments made to the disclosure. See MPEP § 2163.06 which states, when filing an amendment, an applicant should show support in the original disclosure for new or amended claims (See MPEP § 714.02 and § 2163.06).

Applicant is required to cancel the new matter in the reply to this Office Action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
July 19, 2005

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Applicants Copy

Sequence comparison (alignment)

GenCore version 5.1.6

OM nucleic - nucleic search, using sw model

Run on: July 14, 2005, 16:47:20 ; Search time 2 Seconds
(without alignments)
3.201 Million cell updates/sec

Title: AF099031
Perfect score: 1569
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Gapop 10.0 , Gapext 0.5

Searched: 1 seqs, 2040 residues

Total number of hits satisfying chosen parameters: 2

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 1 summaries

Database : af059203.gb_pr:*

Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

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ALIGNMENTS

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DEFINITION Homo sapiens acyl coenzyme A:cholesterol acyltransferase 2 mRNA, complete cds.
ACCESSION AF059203
VERSION AF059203.1 GI:3746534
KEYWORDS .
SOURCE Homo sapiens (human)
ORGANISM Homo sapiens
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE 1 (bases 1 to 2040)
AUTHORS Oelkers,P., Behari,A., Cromley,D., Billheimer,J.T. and Sturley,S.L.
TITLE Characterization of two human genes encoding acyl coenzyme A:cholesterol acyltransferase-related enzymes
JOURNAL J. Biol. Chem. 273 (41), 26765-26771 (1998)
MEDLINE 98434592
PUBMED 9756920
REFERENCE 2 (bases 1 to 2040)
AUTHORS Oelkers,P., Cromley,D., Behari,A., Billheimer,J.T. and Sturley,S.L.
TITLE Direct Submission
JOURNAL Submitted (13-APR-1998) Human Nutrition, Columbia University, 630 W. 168th Street, New York, NY 10032, USA
FEATURES Location/Qualifiers
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Query Match 99.7%; Score 1564.2; DB 1; Length 2040;
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Matches 1566; Conservative 0; Mismatches 3; Indels 0; Gaps 0;

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